REMARKS

Applicant requests entry and consideration of the amendment and remarks submitted herein. Applicant has amended the claims that claimed five compounds to the two compounds that show substantial, broad based therapeutic benefit shown in application Table 2.

The amended claims 7, 9-12 generically claim the 2,5-OMe and 2-F compounds administered in an effective multi-drug resistant HIV strain reducing amount to a subject with an identified multi-drug resistant HIV strain. These compounds were claimed as members of a markush group of original claim 2 as filed.

The amended claims 13-17 specifically claim the 2,5-OMe compound administered in an effective multi-drug resistant HIV strain reducing amount to a subject with an identified multi-drug resistant HIV strain. This compound was claimed as a member of a Markush group of original claim 2 as filed.

New claims 18-22 specifically claim the 2-F compound administered in an effective multi-drug resistant HIV strain reducing amount to a subject with an identified multi-drug resistant HIV strain. This compound was claimed as a member of a Markush group of original claim 2 as filed.

Claims 7-22 are currently pending in this application.

Rejections under 35 U.S.C. § 103(a)

Claims 7-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 93/03022 (*Lind et al).* The Examiner asserts that WO 93/03022 teaches the compounds as useful for treating HIV as claimed. The Examiner further asserts that it is generally considered *prima facie* obvious to employ compounds taught as inhibiting viral replication as therapeutic for this same condition. Applicants disagree.

The Examiner has not established a *prima facie* case of obviousness. Applicant submits that WO 93/03022 does not disclose or suggest the claimed method. Further, there is no suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art at the time of filing, to modify the reference. Further still, there is no reasonable expectation of success to treat multi-drug resistant HIV with the two claimed compounds by modifying the reference teachings.

Clearly, WO 93/03022 does not disclose or suggest the treatment of multi-drug resistant HIV as claimed by the Applicant.

The Examiner has provided no motivation to modify WO 93/03022 to suggest treatment of multi-drug resistant HIV with the two claimed compounds. The Examiner has provided no reasonable expectation of success to modify WO 93/03022 to suggest treatment of multi-drug resistant HIV.

The Examiner asserts that:

- The skilled artisan would have seen the selection of those compounds herein recited as the selection from among obvious alternatives.
- The medical practitioner, after employing an ineffective medicament, would employ another medicament to effect positive anti-HIV therapy would have been obvious to the skilled artisan.
- It is generally considered *prima facie* obvious to employ compounds taught as inhibiting viral replication as therapeutic for this same condition.
- The idea of using them flows logically from their having been used individually in the prior art.

Applicants traverse these statements as merely **conjecture, speculation or assumption** and again request the Examiner to cite a reference to support the position in accordance with MPEP 2144.03. Applicants assert that the Examiner has advanced no evidence to support these statements.

WO 93/03022 discloses millions of compounds and specifically discloses thousands of compounds that may inhibit HIV generally. Only HIV-RT was tested. Neither of the claimed compounds nor anything of similar structure was tested by WO 93/03022.

Applicant's Table 2 clearly shows that minor modifications to the claimed compounds' phenyl substitutions greatly alters the compounds therapeutic benefit.

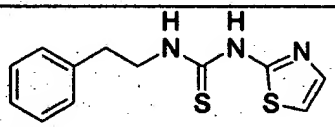
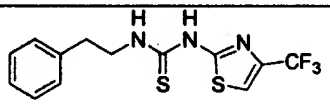
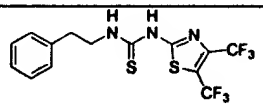
Further, Applicants' data Table 2 illustrates that conventional anti-HIV agents and specifically conventional NNI agents such as **Delavirdine and Nevirapine** are ineffective against multi-drug resistant HIV. The skilled artisan would not expect an NNI agent to be effective since the commercially available NNI agents are simply ineffective against multi-drug resistant HIV as shown in Table 2 of Applicants' specification.

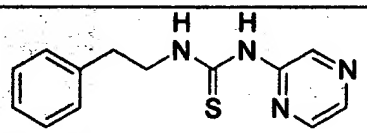
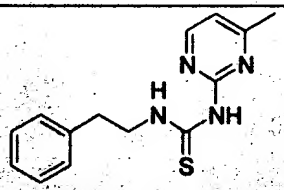
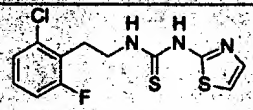
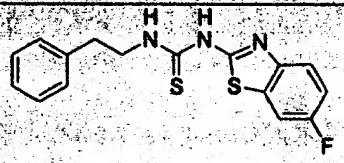
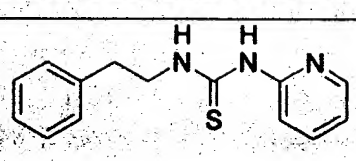
The Examiner's rational is simply an improper "obvious to try" argument to support the rejection. Specifically, the Examiner's statement:

> "The medical practitioner, after employing an ineffective medicament, would employ another medicament to effect positive anti-HIV therapy would have been obvious to the skilled artisan."

requires a medical practitioner to give a terminally-ill HIV patient every compound of the millions disclosed in the cited reference until a compound showed therapeutic benefit. This suggestion is ridiculous. This reference provides no indication of which chemical structure or substitutions thereto out of virtually millions available would likely be successful.

The cited references preferred compound is structurally distinct from the claimed invention. The cited reference's main compound (an unsubsutituted phenethyl thiazolyl thiourea) is found at page 128 and shows inhibition of HIV-RT at 100% for HIV-RT. The only phenethyl pyridyl thiourea tested by WO 93/03022 is at page 133 and is unsubstituted. WO 93/03022 test results (inhibition %) on these and other compounds for HIV-RT follows from Table A1, Table A2 and Table A3 at pages 128-142.

Test Compound	% Inhibition of HIV-RT at below compound concentration			
	100 ug/ml	10 ug/ml	1 ug/ml	0.1 ug/ml
 1-Phenethyl-3-thiazol-2-yl-thiourea	-	100	100	2
 1-Phenethyl-3-(4-trifluoromethyl-thiazol-2-yl)-thiourea	66	24	100	-
 1-(4,5-Bis-trifluoromethyl-thiazol-2-yl)-3-phenethyl-thiourea	99	85	71	-

Test Compound	% Inhibition of HIV-RT at below compound concentration			
	100 ug/ml	10 ug/ml	1 ug/ml	0.1 ug/ml
 1-Phenethyl-3-pyrazin-2-yl-thiourea	100	100	4	-
 1-(4-Methyl-pyrimidin-2-yl)-3-phenethyl-thiourea	100	64	42	-
 1-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-3-thiazol-2-yl-thiourea	100	100	100	-
 1-(6-Fluoro-benzothiazol-2-yl)-3-phenethyl-thiourea	100	100	100	-
 1-Phenethyl-3-pyridin-2-yl-thiourea	6	2	0	-

Clearly, these test results would not inspire the medical practioner to pursue compounds based on a phenethyl pyridyl thiourea backbone especially with substitutions. In addition, these compounds were not tested on multi-drug resistant HIV.

A rejection based on inherency is clearly not appropriate here. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish

the inherency of that result or characteristic. See MPEP 2112. The Examiner has presented no evidence that the result or characteristic alleged inherent necessarily flows from the teaching of the prior art. See MPEP 2112. Both the cited reference and Applicants' Table 2 show that minor modifications to the tested compounds greatly alter the compounds' therapeutic benefit. In addition, Applicants' Table 2 shows that compounds having therapeutic benefit for one form of HIV will not have the same therapeutic benefit for another mutated form of HIV.

Withdrawal of the rejection is respectfully requested.

In view of the above, it is respectfully submitted that claims 7-22 are patentable over the cited reference. Favorable reconsideration is requested.

CONCLUSION

In view of the above, Applicant respectfully requests withdrawal of the rejections and allowance of the claims. Prompt passage to issue is earnestly solicited. Should the Examiner feel a telephone interview would be helpful in advancing this case to allowance, Applicant invites the Examiner to contact their representative at the number listed below.

Respectfully submitted,

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P.O. Box 2903
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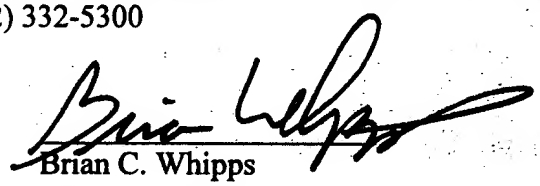
(612) 332-5300

Dated: 1-22-02

By: 
Brian C. Whipps
Reg. No. 43,261
BCW:sms

Version with Markings to Show Changes Made

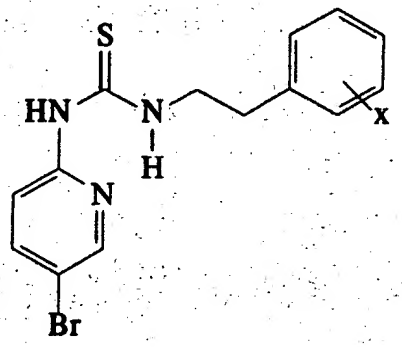
IN THE CLAIMS

Please amend claims 7, 9-17 as follows.

7. (Once Amended) A method comprising:

(a) diagnosing in a subject one or more HIV strain that is resistant to one or more chemotherapeutic agent; and

(b) administering to the subject an effective viral reducing amount of a compound of the formula:

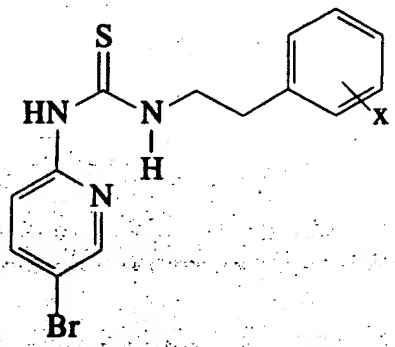


wherein x is: 2,5-OMe~~;~~ or *o*-F~~; *m*-F; *p*-F; or *o*-Cl~~.

9. (Once Amended) A method comprising:

(a) identifying in a subject a mutant form of HIV reverse transcriptase, the mutant form of HIV reverse transcriptase comprising an amino acid substitution at position 106 or 183; and

(b) administering to the subject an effective mutant form of HIV reverse transcriptase reducing amount of a compound of the formula:

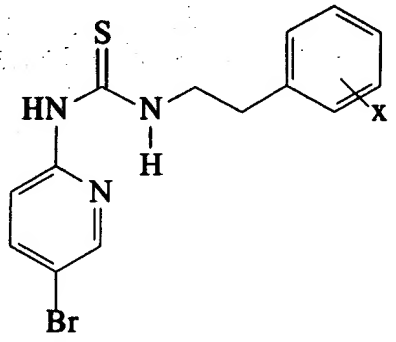


wherein x is: 2,5-OMe~~;~~ or *o*-F~~; *m*-F; *p*-F; or *o*-Cl~~.

10. (Once Amended) A method comprising:

(a) identifying in a subject a mutant strain of HIV having a mutated HIV reverse transcriptase comprising one or more of the following amino acid substitutions: L100I, K103N, V106A, E138K, Y181C, or Y188H; and

(b) administering to the subject an effective mutated HIV reverse transcriptase reducing amount of a compound of the formula:

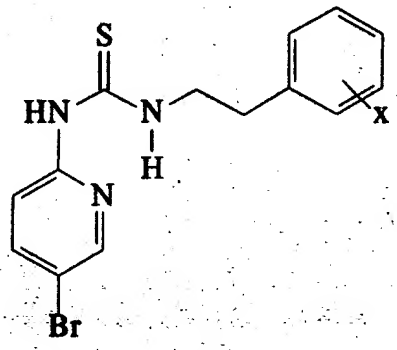


wherein x is: 2,5-OMe~~;~~ or *o*-F~~; *m*-F; *p*-F; or *o*-Cl~~.

11. (Once Amended) A method comprising:

(a) identifying in a subject one or more non-nucleoside inhibitor-resistant strain of HIV; and

(b) administering to the subject an effective non-nucleoside inhibitor-resistant strain of HIV reducing amount of a compound of the formula:

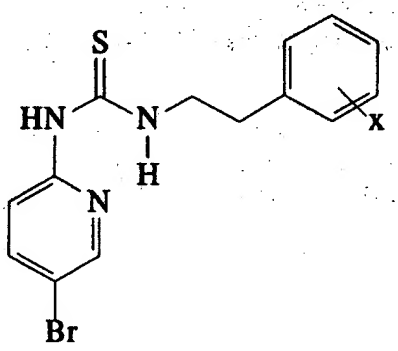


wherein x is: 2,5-OMe~~;~~ or *o*-F~~; *m*-F; *p*-F; or *o*-Cl~~.

12. (Once Amended) A method comprising:

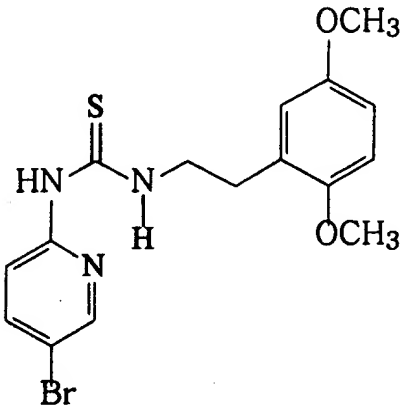
(a) identifying in a subject a mutant HIV strain RT-MDR, A17, A17 variant, or a combination thereof; and

(b) administering to the subject an effective mutant HIV strain RT-MDR, A17, A17 variant, or a combination thereof reducing amount of a compound of the formula:

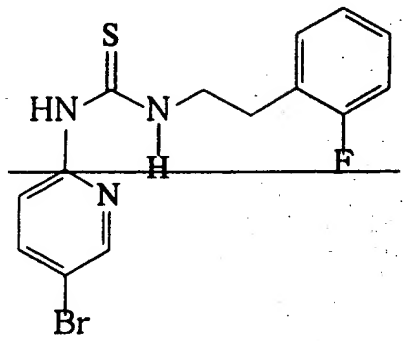


wherein x is: 2,5-OMe~~;~~ or *o*-F~~; *m*-F; *p*-F; or *o*-Cl~~.

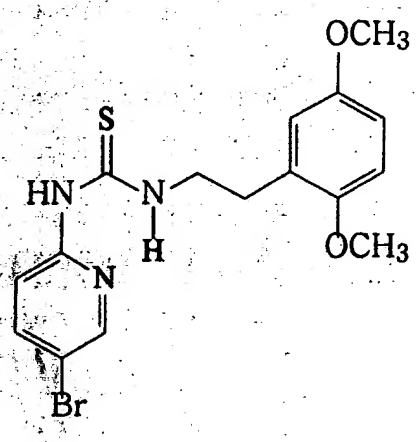
13. (Once Amended) The method of claim 7, wherein said compound is



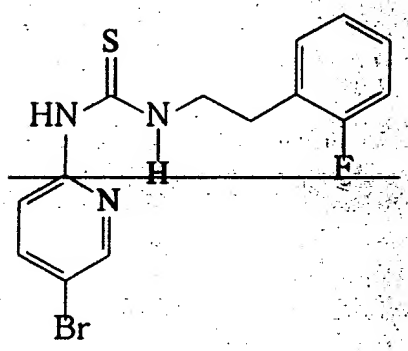
or



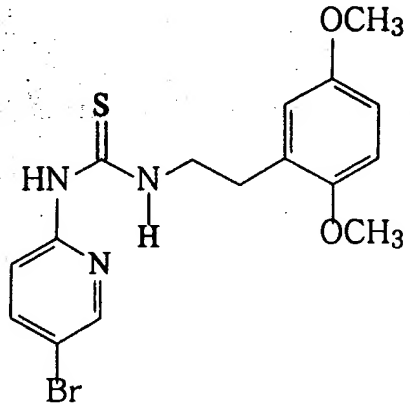
14. (Once Amended) The method of claim 9, wherein said compound is



or



15. (Once Amended) The method of claim 10, wherein said compound is



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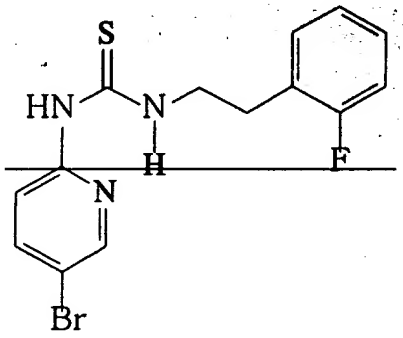
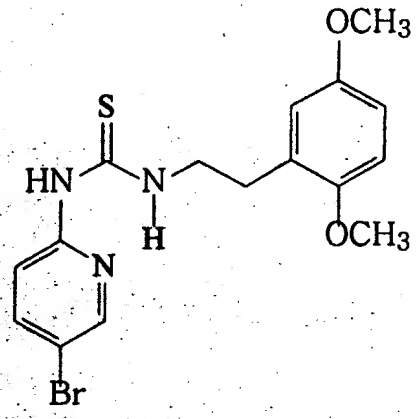
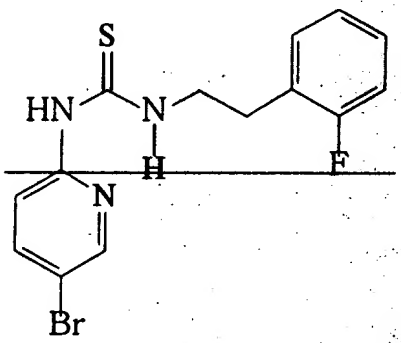


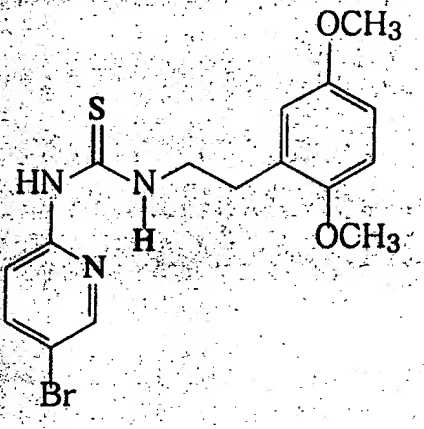
16. (Once Amended) The method of claim 11, wherein said compound is



or



17. (Once Amended) The method of claim 12, wherein said compound is



or